Safety of PVDF-HFP

Biocompatibility studies
Cytotoxicity tests per ISO 10993 were performed on each lot of the polymer and confirmed that the material was non-cytotoxic to mammalian cells. Bioburden and Endotoxin by LAL were also tested on three lots of polymers and passed the test criteria per USP <61> and <85>, respectively.

Additional biocompatibility testing was conducted where non-sterile PBMA and PVDF-HFP cast film was extracted with methanol and the extract was tested for irritation and sensitization in guinea pig per ICH 10993 (this testing was conducted to comply with Japan regulatory requirements). The results showed that the extract did not induce skin reaction in guinea pig.

Biocompatibility studies on Xience™ V EECSS demonstrated that the product conformed to the requirements of ISO 10993 and the USP <87/88> where applicable. The test summaries are in P070015 Module 1 and Module 3 (Module 3 contains carcinogenicity and teratology test results). The following tests were also performed on polymer-only coated stents: cytotoxicity, sensitization, intracutaneous toxicity, acute systemic toxicity, and systemic injection test and 7-day intramuscular implantation in rabbit. All polymer coated stents passed the tests (Table 6-28).

Table 6-28 Summary of Biocompatibility Studies

Sample description	# of lot of polymer	Biocompatible test	Regulatory test	Results
PVDF-HFP pellet	Every lot	Cytotoxicity	ISO 10993	Pass
PVDF-HFP Pellet	3 lots	Bioburden and Endotoxin by LAL	USP<61> and <85>	Pass
PBMA and PVDF-HFP cast film	1 lot	Irritation and sensitization	ISO 10993	Pass
PBMA and PVDF-HFP coated stents	1 lot	Cytotoxicity, sensitization, intracutaneous toxicity, acute system toxicity, system inject test and 7-day intramuscular implantation in rabbit	ISO 10993 and/or USP <87/88>	Pass

Safety studies
Long term animal studies (up to two years) on polymer-only coated stents with up to 3X polymer loading provide further support that PVDF-HFP is safe for the intended application. The vascular response to the PVDF-HFP coated stent with various coating weights at different time points was comparable to the response to a bare metal VISION® stent demonstrating the safety of the polymer coating (P070015 Module 1, Section 7.2).

Stability of PVDF-HFP

Polymer stability from the literature

Poly(vinylidene fluoride) (PVDF) is a fluorinated, semicrystalline thermoplastic polymer obtained by a free radical polymerization of vinylidene fluoride (VDF) using a suspension polymerization process. Copolymerization of VDF with a small amount (<20%) of hexafluoropropylene (HFP) reduces the stiffness and improves the ability to process the material, especially for coating applications without an appreciable loss of chemical resistance.

The backbone of the PVDF-HFP used in the XIENCE® V stent is composed entirely of carbon atoms, with 54% of the carbons bearing fluoro or trifluoromethyl groups, and the remaining 46% bearing hydrogen atoms. Fluoropolymers, especially perfluoropolymers, are among the most chemically inert of organic compounds. Their outstanding resistance to thermal degradation, UV photolysis, and degradation by hydrolysis and oxidation can be attributed to the presence of the fluorine atom. The bond strength of the aliphatic C-F bond (540 kJ/mol) in fully fluorinated hydrocarbons exceeds that of the C-H bond (435 KJ/mol) in aliphatic hydrocarbons (Brady R. F, Fluoropolymers, Chem. in Britain, May, 1990, p. 427-430), which signifies the stability of the pendant fluorine atom. To break the PVDF-HFP backbone, a C-C bond must be cleaved. However, fluorination increases the strength of C-C bonds. For example, the C-C bond in CH3-CH3 is 370 KJ/mole, while the C-C bond strength in CF3-CF3 is 406 KJ/mole. Reactions which might degrade PVDF-HFP represent a kinetic and thermodynamic resolution of bond-making and bond-breaking in favor of the most thermodynamically stable system. For fluoropolymers, most degradation reactions are not thermodynamically favorable unless very high temperatures or strong reducing agents are utilized. The absence of reactive or enzymatically sensitive groups, such as anhydride, ester, amide, ether, ketone, aldehyde, carbonate, or phosphate bonds makes the polymer resistant to hydrolytic, oxidative, or enzymatic cleavage.

Stress stability

A study was conducted to support the stability of PVDF-HFP where three lots of PVDF-HFP were subjected to various stress conditions (oxidation, photo-stress, thermal, and temperature excursion cycle). The study design and stress conditions assessed in the study are provided in Table 6-29. The test methods used in this study are listed in Table 6-29. Each lot was tested in triplicate. Testing was also performed in triplicate on untreated samples (control samples) of the same lots. The results of these studies were summarized in P070015 Module 2, Table 3.2.A.3.S.7-25. All of the data obtained met the proposed PVDF-HFP specifications (Section 3.2.A.3.S.4.1, Specifications for PVDF-HFP) for the tests performed. 19F NMR and FT-IR spectra were compared with the reference PVDF-HFP and no changes of the spectra were discovered within the limit of the test method. No significant differences were observed in the data obtained for the stressed and the control samples indicating that PVDF-HVP is stable under the stress conditions. The test methods used to analyze samples from these stability studies are found in P070015 Module 2, Section 3.2.A.3.S.4.2, Analytical Procedures for PVDF-HFP.

5.1.1 Biocompatibility Studies

Introductory Summary

A series of short-term biocompatibility tests were conducted in compliance with Good Laboratory Practices (GLP) regulations to demonstrate that the materials and components of the XIENCE™ V Everolimus Eluting Coronary Stent System (EECSS) are biocompatible. Tests were conducted on the ethylene oxide-sterilized XIENCE V Rapid Exchange (RX) EECSS, XIENCE V Over the Wire (OTW) EECSS, or variations consisting of the stent component alone. These configurations are representative of the materials and components of the XIENCE V product intended for commercialization. **Table 5-2** below provides a summary of the configurations tested and nomenclature used throughout this section.

Table 5-2 Description of the XIENCE V Test Articles

Configuration	Article Description	Nomenclature
Stent & Delivery System (conducted for OTW platform only)	• Cobalt chromium stent[1] • PBMA primer layer (92 µg/cm^2) • 100 µg/cm^2 everolimus in PVDF-HFP (D:P 1:4.9)[2] • XIENCE™ V OTW Delivery System	XIENCE V Stent and OTW delivery system
Stent & Delivery System (conducted for RX platform only)	• Cobalt chromium stent[1] • PBMA primer layer (92 µg/cm^2) • 260 µg/cm^2 everolimus in PVDF-HFP (D:P 1:4.0) • XIENCE™ V Rapid Exchange (RX) Delivery System	2.6X Stent and RX delivery system
Stent Component Alone	• Cobalt chromium stent[1] • PBMA primer layer (92 µg/cm^2) • 260 µg/cm^2 everolimus in PVDF-HFP (D:P 1:4.0)	2.6X XIENCE V Stent
	• Cobalt chromium stent[1] • PBMA primer layer (92 µg/cm^2) • 100 µg/cm^2 everolimus in • PVDF-HFP (D:P 1:4.9)	XIENCE V Stent

There are slight differences in the materials comprising the RX and OTW delivery system platforms; however, the coated stent and the materials it contacts are identical between the systems. Due to the small differences in the delivery system materials, biocompatibility tests that included the delivery system platform were repeated for the OTW platform. Tests that evaluated the stent component only (without the delivery system) were not repeated as the coated stent is identical among both delivery system platforms.

[1] Based on the MULTI-LINK VISION® or MULTI-LINK MINI VISION™ (Canada License #62845) stents.

Biocompatibility testing was initiated in 2003 prior to the clinical dose selection of 100 $\mu g/cm^2$. Therefore, the highest dose under consideration for clinical evaluations, 260 $\mu g/cm^2$, herein referred to as the "2.6X stent and delivery system" and/or "2.6X XIENCE V stent", was selected for biocompatibility testing. The 2.6X stent and RX delivery system and/or 2.6X XIENCE V stent was selected for testing because it contained all the materials and components of the doses under consideration and contained the maximum total amount of drug.

Abbott Vascular had high confidence in the biocompatibility of the individual components represented in the 2.6X stent and RX delivery system and/or 2.6X XIENCE V stent; based on the fact that VISION/MINI VISION stent delivery systems and the polymers (PBMA and PVDF-HFP) are utilized on commercially available medical devices and everolimus has been investigated in laboratory animals and human clinical trials. Abbott Vascular believes that the dose evaluated is representative of all material and components present on the XIENCE V EECSS intended for commercialization.

Abbott Vascular also conducted two long-term biocompatibility GLP studies utilizing the XIENCE V stent in two different subcutaneous rodent models. A teratology (reproductive toxicity) study was initiated to demonstrate that implantation of the XIENCE V stents in female Sprague-Dawley rats does not affect their fertility or reproductive capability as well as to show a lack of any teratology effect on their offspring. Additionally, a 26-week carcinogenicity study in CB6F1-TgrasH2 (rasH2) mice was initiated to demonstrate that the implant of the XIENCE V stent has no increased carcinogenic potential when compared to controls.

All biocompatibility testing was conducted in accordance with one or more of the following general regulations and guidance documents:

- Guidance for Industry and FDA Staff, Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems; published by the Interventional Cardiology Devices Branch, Division of Cardiovascular Devices, Office of Device Evaluation on January 13, 2005
- Good Laboratory Practices Regulations (21 CFR § 58)
- International Standards ISO-10993 (Biological Evaluation of Medical Devices)
- USP <85> Bacterial Endotoxin Test
- USP <87/88> Biological Reactivity Tests
- USP <161> Transfusion and Infusion Assemblies and Similar Medical Devices

All biocompatibility testing met the applicable acceptance criteria for both the Over-the-Wire (OTW) and Rapid Exchange (RX) delivery systems. These results demonstrate the safety of the delivery system containing the drug eluting stent (XIENCE V Stent and OTW delivery system, 2.6X Stent & RX delivery system)

and two different doses of the everolimus coated stent (2.6X XIENCE V stent, XIENCE V stent).

Nomenclature

Some of the biocompatibility reports written by contract testing labs were in place prior to Guidant Corporations merger agreement with Boston Scientific in which the Vascular Intervention (VI) and Endovascular Solutions (ES) assets were divested to Abbott Laboratories. Therefore, many of the biocompatibility reports refer to the study sponsor as Guidant since this was the official sponsor name at time of study approval. In addition, during the course of testing, Northview Pacific Laboratories changed their name to Pacific BioLabs. The testing reports may reference either test laboratory name.

The nomenclature used to describe the XIENCE V EECSS in the reported biocompatibility studies has changed over the past three years. Initial studies conducted to support the SPIRIT III clinical trial evaluating the 2.6X Stent and RX delivery system and 2.6X XIENCE V stent, cited the test product either as VISION-E or ML VISION-PBMA IDE 3.0 X 18 mm, Everolimus dose = 250 µg/cm2. As defined above, this product consisted of a MULTI-LINK VISION® stent coated with a PBMA primer layer (92 µg/cm2) and 260 µg/cm2 everolimus in PVDF-HFP (D:P 1:4.0) and contained approximately 2.6 times the amount of drug as the current (100 µg/cm2) design. The nomenclature changed from the original drug dose density of 250 µg/cm2 on the test reports, which was the expected theoretical value, to 260 µg/cm2 which is the actual drug density of the product used for testing as confirmed by results of analytical testing.

Biocompatibility Studies and Results

Table 5-2 provides a detailed overview of the biocompatibility studies conducted to support the safety of the XIENCE V product and the results of each study.

Table 5-2 Biocompatibility Testing Overview

Test Name	Description of Test	Test Article and Results
Cytotoxicity	ISO 10993-5: In Vitro Cytotoxicity (L929 MEM Elution)	• XIENCE V Stent and OTW delivery system: Pass (non-cytotoxic) • 2.6X Stent and RX delivery system: Pass (non-cytotoxic)
Sensitization	ISO 10993-10: Sensitization (Guinea Pig Maximization)	• XIENCE V Stent and OTW delivery system: Pass (non-sensitizing) • 2.6X Stent and RX delivery system: Pass (non-sensitizing)
Intracutaneous Reactivity	ISO 10993-10: Irritation (Rabbit Injection)	• XIENCE V Stent and OTW delivery system: Pass (non-irritating) • 2.6X Stent and RX delivery system: Pass (non-irritating)
Systemic Toxicity	ISO 10993-11: Systemic Toxicity, Acute (Mouse Injection)	• XIENCE V Stent and OTW delivery system: Pass (non-toxic) • 2.6X Stent and RX delivery system: Pass (non-toxic)
Pyrogenicity	Bacterial Endotoxin (LAL)	• XIENCE V Stent and OTW delivery system: Pass (non-pyrogenic) • 2.6X Stent and RX delivery system: Pass (non-pyrogenic)
	ISO 10993-11: Systemic Toxicity (Material Mediated Rabbit)	• XIENCE V Stent and OTW delivery system: Pass (non-pyrogenic) • 2.6X Stent and RX delivery system: Pass (non-pyrogenic)
Hemocompatibility/ Hemolysis	ISO 10993-4: Hemolysis, Indirect Contact (Rabbit Red Blood Cells)	• XIENCE V Stent and OTW delivery system: Pass (non-hemolytic)
	ISO 10993-4: Hemolysis, Direct Contact (Rabbit Red Blood Cells)	• 2.6X Stent and RX delivery system: Pass (non-hemolytic)
	Thrombosis (fulfilled through Hemolysis and *in vivo* animal testing)	• XIENCE V Stent and OTW delivery system: Pass (non-hemolytic) • 2.6X Stent and RX delivery system: Pass (non-hemolytic)
	ISO 10993-4: Clotting, PT (Human Plasma)	• XIENCE V Stent and OTW delivery system: Pass (non-hemolytic) • 2.6X Stent and RX delivery system: Pass (non-hemolytic)
	ISO 10993-4: Partial Thromboplastin Time, PTT (Human Plasma)	• XIENCE V Stent and OTW delivery system: Pass (non-hemolytic) • 2.6X Stent and RX delivery system: Pass (non-hemolytic)
Implantation	ISO 10993-6: 90-day (Rabbit, Intramuscular)	• 2.6X XIENCE V stent: Pass
	Sub-chronic Toxicity (fulfilled through 90-day implant)	

Table 5-2 Biocompatibility Testing Overview (cont'd)

Test Name	Description of Test	Test Article and Results
Genotoxicity	ISO 10993-3: Bacterial Reverse Mutation Assay (Ames test)	• 2.6X XIENCE V stent: Pass (non-mutagenic)
	ISO 10993-3: *In Vitro* Chromosomal Aberration (Chinese Hamster Ovary cells)	• 2.6X XIENCE V stent: Pass (non-mutagenic)
	ISO 10993-3: Clastogenicity in Mammalian Cells (CHO/HGPRT forward mutation)	• 2.6X XIENCE V stent: Pass (non-mutagenic)
	ISO 10993-3: Mammalian Erythrocyte Micronucleus Test	• 2.6X XIENCE V stent: Pass (non-mutagenic)
Reproductive Toxicity (Teratology)	ISO 10993-3: Reproductive and Developmental Toxicity	• XIENCE V stent: Pass (non-teratogenic)
Carcinogenicity	ISO 10993-3: Carcinogenicity	• XIENCE V stent: Pass (non-carcinogenic)

Following are brief descriptions of each of the biocompatibility test methods used for evaluation of the XIENCE V product.

Cytotoxicity

The cytotoxicity tests were either conducted at Northview Pacific Laboratories (previously known as Northview Laboratories) or at the Guidant Cardiac Rhythm Management (now Boston Scientific, St. Paul, MN) microbiology lab in accordance with ISO 10993-5. The cytotoxicity test is an *in-vitro* tissue culture test that evaluates the biological reactivity of mammalian cell cultures (L-929 mouse fibroblasts). Cell cultures were put into contact either directly with the polymeric material or indirectly with specific extracts prepared from the material under test. The test samples were extracted using MEM which is a physiological growth medium for mammalian cell culture supplemented with serum for 24 hours at 37°C in a humidified incubator containing 5 ± 1% of carbon dioxide. The cell culture was exposed to the extract for 48 ± 2 hours at 37 ± 1°C in a humidified incubator containing 5 ± 1% of carbon dioxide and then evaluated for toxicity. The cytotoxic response of the test sample was measured by percent cell lysis with an acceptance criterion of not cytotoxic.

Sensitization

The sensitization test was conducted at Northview Pacific Laboratories in accordance with ISO 10993-10. The sensitization test, based on the Guinea pig maximization test of Magnusson and Kligman, was intended to determine the potential of the polymeric material under test or with specific extracts of the material under test to elicit contact dermal allergenicity in guinea pigs. Test samples were extracted using sodium chloride for injection (SCI) and Cotton Seed

Oil (CSO) at 50°C for 72 hours. Each sample extract was used by itself and in a 50:50 combination with Freund's Complete Adjuvant (FCA).

The animals were wrapped in the same manner as for the topical application of the induction phase except that light rubber sheeting was not used since the Hill Top Chambers™ provided the necessary occlusion. Twenty four (24) hours after dosing, the animals were unwrapped. The dosing sites for the SCI test group and SCI negative controls were allowed to air dry. The dosing sites for the positive controls and naïve positive controls and CSO test group and its control were gently cleansed with 70 % ethanol to remove any chemical residues.

All the animals were observed for adverse reactions immediately after dosing and daily until the end of the study. The skin at the challenge dosing sites was scored for skin reaction at 24 ± 2 hours and at 48 ± 2 hours after unwrapping and scored on a scale of 0 to 3. The acceptance criteria of the test are that the test sample meets the requirements of the test if the reaction scores received by the test group are no different than control. Any test animal showing a reaction score greater than the negative control group is considered to represent significant sensitization.

Intracutaneous Reactivity (Irritation)

The Intracutaneous Reactivity test was conducted at Northview Pacific Laboratories in accordance with ISO 10993-10. This test is designed to evaluate the local biological responses of animals to polymeric material under test or to the extracts of materials under test following a single intracutaneous injection, along the spinal column, into three rabbits. The samples were extracted with SCI and CSO at 50°C for 72 hours. Five (5) sites of the rabbits were injected intracutaneously with 0.2 mL of SCI and the other five (5) sites were injected intracutaneously with 0.2 mL of CSO and an additional five (5) sites for the control for a total of ten (10) test sites and five (5) control sites. This was repeated using all three rabbits. The animals were observed at 24, 48 and 72 hours after injection for both erythema and edema formation which was measured on a scale of zero (0) to four (4) and compared to control. The primary irritation index (PII) was determined by summing the scores of all of the animals and dividing by the number of animals. The test sample meets the requirements of the test if the total score for the PII is negligible (0.0 - 0.4) or slight (0.5 – 1.9).

Acute Systemic Toxicity (System Injection, Acute)

The acute systemic injection test was conducted at Northview Pacific Laboratories in accordance with ISO 10993-11. This test is designed to evaluate systemic responses to the extracts of materials under investigation following a single injection into mice. The samples were extracted each with SCI and CSO at 50°C for 72 hours. The CSO extract is injected intraperitoneally. Five (5) mice each were injected (with 50 mL/kg body weight) for the CSO test sample extract and CSO blank for a total of ten (10) mice per media type. This was conducted intravenously for the SCI extract test media for a total of 20 mice for both extract media types. The animals were observed immediately after the injection and at 4, 24, 48 and 72 hours respectively.

The sample meets the requirements of the test if, during the observation period, none of the mice treated with the extract of the sample show a significantly greater biological reactivity than the mice treated with the blank. If two or more mice die, or if abnormal behaviors such as convulsions or prostration occurs in two or more mice, or if a body weight loss greater than 2 g occurs in three or more mice, the sample does not meet the requirements of the test.

Pyrogenicity - LAL Bacterial Endotoxin

The LAL Bacterial Endotoxin test was conducted at Abbott Vascular. This test determined the concentration of bacterial endotoxins that may be present in or on the sample of the test article to which the test is applied using Limulus Amebocyte Lysate (LAL) which has been obtained from aqueous extracts of the circulating amebocytes of the horseshoe crab, *Limulus polyphemus*, and which has been prepared and characterized for use as an LAL reagent for gel-clot formation. This test was performed by the gel clot method. The entire device was extracted in 40 mL of WFI (water for injection) at room temperature for 60 minutes. The device passes the test if the endotoxin units present in the sample are less than 0.5 EU/mL.

Pyrogenicity - Material Mediated Pyrogen (Rabbit)

The Material Mediated Pyrogen test was conducted at Northview Pacific Laboratories in accordance with ISO 10993-11, Section 7.1. The material mediated pyrogen test determined the febrile reaction of the test animal to the administration by injection, of an extract of the test sample. The test samples were extracted with sodium chloride for injection (SCI) at 50°C for 72 hours.

The test involved measuring the rise in temperature of the rabbits following the intravenous injection of the extract which is designed for products that can be tolerated by the test rabbit in a dose not to exceed 10 mL per kg injected intravenously within a period of not more than 10 minutes. Three (3) test rabbits and three (3) controls were used for the test for a total of six (6) rabbits.

The product meets the requirements for the absence of pyrogen if no rabbit shows an individual rise in temperature of 0.5°C or more above its respective control temperature.

Hemocompatibility - Hemolysis

The hemolysis tests were conducted at Northview Pacific Laboratories in accordance with ISO10993-4. Hemolysis is defined as the liberation of hemoglobin from erythrocytes, either by destruction or through the partially damaged but intact cell membrane. The hemolysis test was performed by the direct contact and indirect contact methods respectively. For the direct contact method, the material under test were placed in a test tube with the addition of SCI and this was exposed to 10% whole blood and incubated at 37 ± 2°C for not less than 180 minutes. For the indirect contact method, the material under test was extracted in SCI for 72 hours at 50°C before the

addition of 10% whole blood. The material under test meets the requirement of the hemolysis test if the percent lysis is less than 5%.

Hemocompatibility -Thrombosis

The thrombosis evaluation is fulfilled through the combination of the Hemolysis described above and the *in vivo* animal study histological evaluation as provided in the *In Vivo* Animal Studies section.

Hemocompatibility - Clotting Time/Coagulation

The coagulation test was subcontracted to Nelson Labs by Northview Pacific Laboratories and tested by Nelson Labs in accordance with ISO 10993-4. The coagulation test consisted of two parts, the Prothrombin Time (PT), and the Partial Thromboplastin Time (PTT). The PT evaluates the extrinsic pathway while the PTT evaluates the intrinsic pathway of the coagulation cascade.

For the PT test, 8.1 cm^2 of test device or control device was incubated in 2.7 mL human plasma at room temperature for 60 minutes. A 0.2 mL aliquot of extract plasma was transferred to each tube. Samples and controls were incubated at 37 ± 1°C and then 0.4 mL of PT reagent with calcium chloride was added and the clotting time determined.

For the PTT tests, samples and controls were extracted as in the PT test. A 0.2 mL aliquot of extract plasma was transferred to each tube. Samples and controls were incubated at 37 ± 1°C and then 0.4 mL of PTT reagent and 0.2 mL of calcium chloride was added and the clotting time determined.

The clotting times for the test samples were compared to the clotting times of the controls based on the type of test performed (PT or PTT). The material under test meets the requirement of the test if there is no significant difference in the clotting time between the test and control samples.

Implantation – 90-day Chronic Toxicity

The Implantation test was conducted at Northview Pacific Laboratories in accordance with ISO 10993-6. The implantation test is designed for the evaluation of plastic materials and other polymeric materials in direct contact with living tissue. This test can be performed with durations of 7, 30, 60 or 90 days with the 90-day length of the implant fulfilling the requirement for sub-chronic toxicity. Histopathology is required for test articles implanted for greater than 7 days.

Two rabbits are typically used for the test with the requirement of implantation of four test strips each measuring 1 x 10 mm into the paravertebral muscle on one side of the spine of the rabbit. In a similar fashion, two (2) strips of USP reference standard, HDPE were implanted in the opposite muscle of each animal. After exposure, the implant site is evaluated on a scale of 0 to 4. The requirements of the test are met if the difference in the average scores of the sample and control sites do not exceed 1, or the

difference between the sample and control mean scores for more than one of the four implant sites does not exceed 1 for any implanted animal.

Implantation - Sub-Chronic Toxicity Test

The Sub-Chronic Toxicity is fulfilled through the 90-day implant with histopathology as described above. The Implantation test was conducted at Northview Pacific Laboratories in accordance with ISO 10993-11. The Sub-Chronic Toxicity test evaluated the adverse effects occurring after the administration of multiple doses of a test sample during part of the lifespan (usually 90 days but not exceeding 10% of the lifespan) of the test animal. Solid materials may be used directly without extraction since they provide continuous exposure over a 90-day period.

Genotoxicity

Genotoxicity testing was conducted by Toxikon in accordance to ISO 10993-3. Genotoxicity tests use mammalian or non-mammalian cells, bacteria, yeasts or fungi to determine whether gene mutations, changes in chromosome structure, or other DNA or gene changes are caused by the test samples. The genotoxicity of a medical device has to be experimentally assessed, using a series of *in vitro* tests. This series includes at least three assays. At least two of these should use mammalian cells as a target.

The first three *in vitro* assays include:

- Bacterial Reverse Mutation Assay, a test for gene mutations in bacteria, ie, AMES test (OECD 471)
- Clastogenicity in Mammalian Cells, a test for gene mutations in mammalian cells, ie, Forward Mutation CHO/HGPRT (OECD 476)
- *In Vitro* Chromosomal Aberration, a test for clastogenicity in mammalian cells, ie, Chrom Ab/CHO cells, (OECD 473).

If any of the three *in vitro* tests are positive, further clarification of mutagenic potential is required using an *in vivo* test with somatic cells. Historically, Abbott Vascular performs the *in vivo* test along with the *in vitro* regardless of sample failure. The *in vivo* test is the:

- *In Vivo* Micronucleus Test, a mammalian erythrocyte micronucleus test in rodents (OECD 474).

(1) Bacterial Reverse Mutation Assay (gene mutations in bacteria), ie, AMES test (OECD 471). The bacterial reverse mutation test uses amino acid deficient strains of *S. typhimurium* and *E. coli*. The standard test strains were developed by Dr. Bruce Ames for detection of point mutations by base substitutions or frame-shifts in the genome of the bacterial tester strains. Most experiments will give clearly positive or negative results as interpreted by the specific protocol used for the test.

(2) Clastogenicity in Mammalian Cells (gene mutations in mammalian cells), ie, Forward Mutation CHO/HGPRT (OECD 476). Gene mutations and mutation frequency are determined using mammalian cells deficient in thymidine kinase (TK), hypoxanthine-guanine phosphoribosyl transferase (HPR), and a transgene of

xanthine-guanine phosphoribosyl transferase (XPRT). Most experiments will give clearly positive or negative results as interpreted by the specific protocol used for the test.

(3) *In Vitro* Chromosomal Aberration (clastogenicity in mammalian cells), ie, chromosomal aberration, (OECD 473). An established cell line (eg, Chinese hamster fibroblasts, human or other mammalian peripheral blood lymphocytes) is exposed to extracts of the device for predetermined intervals. Cell division is arrested in metaphase for microscopic evaluation of chromosomal aberrations, polyploidy and endoreduplication.

(4) *In Vivo* Micronucleus Test, ie, mammalian erythrocyte micronucleus test in rodents (OECD 474). Appropriate rodent species, usually mice or rats, are exposed to extracts of the device for predetermined intervals. Preparations of bone marrow or peripheral whole blood are analyzed for the presence of micronuclei. The mammalian *in vivo* micronucleus test is used for the detection of damage induced by the test substance to the chromosomes or the mitotic apparatus of erythroblasts by analysis of erythrocytes as samples in bone marrow and/or peripheral blood cells of animals. The purpose of the micronucleus test is to identify substances that cause cytogenic damage which results in the formation of micronuclei containing lagging chromosome fragments or whole chromosomes. When the bone marrow erythroblast develops into a polychromatic erythrocyte, the main nucleus is extruded; any micronucleus that has been formed may remain behind in the otherwise anucleated cytoplasm. Visualization of micronuclei is facilitated in these cells because they lack a main nucleus. An increase in the frequency of micronucleated polychromatic erythrocytes in treated animals is an indication of induced chromosome damage. Most experiments will give clearly positive or negative results as interpreted by the specific protocol used for the test.

Teratology

The reproductive toxicity/teratology study was conducted at Toxikon Corporation (Bedford, Massachusetts) in accordance with ISO 10993-3. Sprague-Dawley rats were implanted subcutaneously with either two XIENCE™ V stents or with two plastic coupons as a negative control fourteen days before being paired with male rats of the same breed for the purpose of mating. Each female was observed once daily for signs of toxicity. Signs of toxicity included but were not limited to changes in skin, fur, eyes, and mucous membranes, changes in respiratory system, circulatory system, autonomic central nervous system (seizures, tremors, and salivation), somato–motor activity, behavior pattern, and diarrhea. Each animal was observed twice daily (a.m. and p.m.) for mortality and morbidity.

Approximately 24 hours prior to delivery, the dams were euthanized, exsanguinated, and caesarian sections were performed. Each uterine horn was opened to expose fetuses and any resorptions. The relative position and condition (live, dead, or resorbed) of all fetuses and implantation sites within each uterine horn were counted. The live fetuses were removed, weighed, sexed, and examined for gross

malformations. To discover visceral abnormalities, half of the fetuses were randomly selected to undergo gross necropsy. The remaining fetuses in each litter were eviscerated, dehydrated in ethanol, cleared in potassium hydroxide, stained with Alizarin Red S, and the skeleton was evaluated.

Carcinogenicity

The carcinogenicity study was conducted at Toxikon Corporation (Bedford, Massachusetts) in accordance with ISO 10993-3. CB6F1-TgrasH2 mice were implanted subcutaneously with a single XIENCE V stent, a negative control, a positive control, or an experimental positive control. Each animal was examined for clinical signs of toxicity twice daily as well as for morbidity/mortality as a part of the daily clinical observations. Animals whose condition made them unlikely that they would survive until the next observation, based upon the criteria (eg, rapid weight loss, any condition interfering with eating, drinking, bleeding from any orifice, loss of mobility, rough hair coat) established by the study director in concert with the veterinary staff and toxicologist, were euthanized immediately, and submitted for necropsy.

All animals were sacrificed at the end of the 26 – 27 week exposure duration by carbon dioxide (CO_2) inhalation, and a necropsy was performed immediately. The gross necropsy observations included examination of the external surface of the body, all orifices, and the cranial, thoracic, and abdominal cavities and their contents. Organ weights were obtained for after trimming of any adherent tissue.

The tissues and organs, tissue lesions, and gross abnormalities were harvested and fixed in 10 % buffered formalin. Following fixation, the tissue samples from all animals, including any gross lesions and abnormalities from all groups were processed for histology and stained with hematoxylin and eosin (H&E). The slides were evaluated and graded by light microscopic examination by a board-certified veterinary pathologist.

Conclusions

All biocompatibility testing met the applicable acceptance criteria for both the Over-the-Wire (OTW) and Rapid Exchange (RX) delivery systems. These results demonstrate the safety of the delivery system containing the drug eluting stent (XIENCE V Stent and OTW delivery system, 2.6X Stent & RX delivery system) and two different doses of the everolimus coated stent (2.6X XIENCE V stent, XIENCE V stent). The biocompatibility studies conformed to the requirements of ISO 10993.

The XIENCE V Stent and OTW delivery system passed all of the short-term biocompatibility tests for externally communicating devices, contacting circulating blood, for a limited (<24 hour) contact duration. These tests included:

- Cytotoxicity
- Sensitization
- Intracutaneous Reactivity
- Acute Systemic Test
- Pyrogenicity

  - Bacterial Endotoxin (LAL)
  - Material Mediated
- Hemocompatibility
  - Hemolysis
  - Coagulation (PT & PTT)

The 2.6X Stent & RX delivery system passed all of the short-term biocompatibility tests for externally communicating devices, contacting circulating blood, for a limited (<24 hour) contact duration. These tests included:

- Cytotoxicity
- Sensitization
- Intracutaneous Reactivity
- Acute Systemic Test
- Pyrogenicity
  - Bacterial Endotoxin (LAL)
  - Material Mediated
- Hemocompatibility
  - Hemolysis
  - Coagulation (PT & PTT)

The 2.6X XIENCE V stent evaluated passed all of the tests required for permanent implants. These tests included:

- Implantation/ Intramuscular, 90 days, with histopathology (subchronic toxicity)
- Genotoxicity
  - Gene mutations in bacteria (Ames Test), OECD #471
  - Gene mutations in mammalian cells (chromosomal aberration), OECD #473
  - Test for clastogenicity in mammalian cells (CHO/HGPRT), OECD #476
  - Mammalian erythrocyte micronucleus test, OECD #474

Additional long-term tests were performed on the XIENCE V Stent. These tests evaluated the fertility, reproductive capability, *in utero* mortality, and carcinogenicity of a the implant.

- Teratology
- Carcinogenicity

All biocompatibility testing met the applicable acceptance criteria for both the Over-the-Wire (OTW) and Rapid Exchange (RX) delivery systems. These results demonstrate the safety of the delivery system containing the drug eluting stent (XIENCE V Stent and OTW delivery system, 2.6X Stent & RX delivery system) and two different doses of the everolimus coated stent (2.6X XIENCE V stent, XIENCE V stent).

A detailed description of each test, the results, and the analyses of data are presented in the test reports included in **Attachment C**.

FDA Panel Meeting re: Late Stent Thrombosis and DES
Master Response Document

Key Messages:

- *Drug-eluting stents benefit thousands of patients each year.*
  - Drug-eluting stents are more effective than bare metal stents at decreasing restenosis (re-narrowing of the vessel), which can lead to increased MI and death.
  - Drug-eluting stents significantly reduce the need for reintervention -- repeat procedures to treat this re-narrowing -- which carries additional risk to patients, including infection and potential complications of surgery

- *Next-generation drug-eluting stents – such as XIENCE V – hold promise for improvements in safety and efficacy over drug-eluting stents currently on the market.*
  - DES products and medical practice are evolving – just as they did when both angioplasty and bare metal stents were introduced.
  - We may have an opportunity with next-generation solutions to improve upon current technology and medical practice that will advance patient care over time.
  - Preclinical evidence suggests that on near-term as well as long-term safety, there may be differences between first- and second-generation DES.
  - The clinical data from SPIRIT I (60 patients OUS) and SPIRIT II (300 patients, EU and Asia-Pacific) support our pre-clinical data:
    - SPIRIT II – superior to TAXUS on in-stent late loss at six months
    - SPIRIT First – 2 year follow up demonstrates long-term safety – No acute, sub-acute or late stent thrombosis
    - FDA will be reviewing longer-term XIENCE V clinical data – out to three years
    - We look forward to sharing additional research results on XIENCE V in the first half of 2007

- *Not all drug-eluting stents are the same.*
  - Each factor associated with the system – the drug that is used, the rate of elution, the polymer coating, the stent platform and the delivery system – is important in overall clinical outcomes.
    - Each element of the Xience system contributes to healthy, complete healing:
      Drug: everolimus drug with anti-proliferative and anti-inflammatory properties.
      Polymer **Coating:** ultra-thin, biocompatible fluoropolymer with excellent integrity designed for safety and efficacy
      Elution: controlled drug release by design
      Platform: VISION platform, built on the proven Multi-Link design, is best-in-class BMS. Cobalt chromium technology, outstanding flexibility and comformability, and excellent deliverability. The worldwide marketing leading BMS with extensive physician experience. Thin struts = minimal injury.

- *The use of DES technology is supported with robust pre-clinical, clinical and real-world post-market patient data.*
  - Abbott's SPIRIT family of trials for XIENCE V will evaluate more than 10,000 patients worldwide with long-term (up to five years) follow-up.
  - We are committed to long-term follow-up of the patients in our studies for years to come

- *The FDA panel meeting will be an important forum for the FDA, physicians and industry to discuss the role of DES in treating patients with coronary artery disease.*

Additional FDA Panel/DES Responses:

Presentation at the panel meeting:

- Krishna Sudhir, M.D., Medical Director, Global Clinical Science for Abbott Vascular's Cardiac Therapies business, will make a general 10-minute presentation to the panel.
- The presentation will include general information about Abbott's DES program, including previously presented preclinical and clinical data regarding XIENCE V.

Potential outcome of the FDA panel meeting (for inquiries in advance of meeting):

- The FDA panel meeting will be an important forum for the FDA, physicians and industry to discuss the role of DES in treating patients with coronary artery disease.
- We hope the panel recognizes that DES help thousands of patients each year and that next-generation technology holds great promise.
    - DES products and medical practice are evolving – just as they did when both angioplasty and bare metal stents were introduced.
    - We have an opportunity with next-generation solutions to improve upon current technology and medical practice to advance patient care over time.
- *[If pressed:* We expect that there will be discussion of the root cause of LST, use of antiplatelet drugs after DES implants, proper patient selection and continuation of long-term follow up/registries.]

Plavix/clopridogrel use:

- Duration of and compliance with Plavix/clopridogrel use is part of the DES equation that needs further study, and more emphasis must be placed on compliance.
- Our current label in Europe recommends that physicians make the determination as to length of antiplatelet therapy individually with their patients.

Clopridogrel/Plavix use in SPIRIT trials:

- In SPIRIT III, the recommended clopridogrel/Plavix duration is six months (same as for the comparator, TAXUS).
- We plan to obtain better measures of clopridogrel/Plavix compliance, and possibly clopridogrel/Plavix and aspirin resistance, in future trials.

Stronger label warnings/greater restriction of types of patients appropriate for DES:

- With the knowledge of robust pre-clinical, clinical and real-world post market data at their disposal, the training and expertise of physicians puts them in the best position to make decisions regarding the appropriate use of device therapies for their patients.
- DES benefit thousands of patients each year, and are more effective than bare metal stents in preventing restenosis and reintervention -- both of which carry their own risks to patients, including potential infection and open heart surgery complications.

- Abbott is committed to long-term follow-up of the patients in our studies for years to come.

Need for longer-term data prior to approval:

- Medical technology advances are achieved in an iterative fashion, building on the best therapies of today to make new and better therapies for tomorrow.
- Next-generation drug-eluting stents hold promise for improvements in safety and efficacy over drug-eluting stents currently on the market.
  - DES products and medical practice are evolving – just as they did when angioplasty and bare metal stents were introduced.
  - We have an opportunity with next-generation solutions to improve upon current technology and medical practice and the potential to advance patient care .
- The use of DES technology is supported with a combination of robust pre-clinical, clinical and real-world post-market patient data.
  - Abbott's SPIRIT family of trials for XIENCE V will evaluate more than 10,000 patients worldwide with long-term (up to five years) follow-up
  - We are committed to long-term follow-up of the patients in our studies for years to come.

Need for post-market registries/long-term follow-up:

- The use of DES technology is supported with robust pre-clinical, clinical and real-world post-market patient data.
- Abbott is committed to long-term follow-up of the patients in our studies for years to come.
  - Abbott's SPIRIT family of trials for XIENCE V will evaluate more than 10,000 patients worldwide with long-term (up to five years) follow-up.
  - Abbott rigorously monitors product safety through worldwide surveillance programs and provides regular safety updates to the FDA.
- Abbott also is supporting the extension of the STENT (**S**trategic **T**ranscatheter **E**valuation of **N**ew **T**herapies) registry
  - Largest prospective, comparative real-world DES study ever reported in the U.S.
  - More than 10,000 patients will be enrolled, with the goal of better understanding the risk factors for the rare occurrences of late stent thrombosis (why raise another red flag with "early" if everyone is focused on "late")
  - Initiated in 2003 to evaluate long-term efficacy and safety of paclitaxel-eluting and sirolimus-eluting coronary stents among real-world patients and clinical situations
  - STENT registry has been extended to include examination of stent thrombosis

DES safety:

- Drug-eluting stents have been shown to benefit tens of thousands of clinical trial patients and millions of real-world patients, over many years.
  - DES are more effective than bare metal stents at decreasing restenosis (re-narrowing of the vessel), which can lead to increased MI and death.

- DES also significantly reduce the need for reintervention -- repeat procedures to treat this re-narrowing -- which carries additional risk to patients.
- The risk of LST with DES must be better understood, and Abbott is committed to long-term careful follow-up of the patients in our studies for years to come.
- Abbott also is supporting the extension of the STENT (**S**trategic **T**ranscatheter **E**valuation of **N**ew **T**herapies) registry
  - Largest prospective, comparative real-world DES study ever reported in the U.S.
  - More than 10,000 patients will be enrolled, with the goal of better understanding the risk factors for the rare occurrences of early and late stent thrombosis
  - Initiated in 2003 to evaluate long-term efficacy and safety of paclitaxel-eluting and sirolimus-eluting coronary stents among real-world patients and clinical situations
  - STENT registry has been extended to include examination of stent thrombosis

LST incidences with XIENCE V:

- We have seen encouraging safety data in our clinical trials so far:
  - SPIRIT FIRST: No thrombosis in either XIENCE V or VISION control group out to two years
  - SPIRIT II: One thrombosis in XIENCE V group (0.5%)

Differentiation of XIENCE V:

- Next-generation drug-eluting stents – such as XIENCE V – hold promise over drug-eluting stents currently on the market.
  - Preclinical evidence suggests that on near-term as well as long-term safety, there may be differences between first- and second-generation DES.
  - The clinical data from SPIRIT I (60 patients OUS) and SPIRIT II (300 patients, EU and Asia-Pacific) support our pre-clinical data:
    - SPIRIT II – superior to TAXUS on late loss at six months
    - SPIRIT First – 2 year follow up demonstrates long-term safety – No acute, sub-acute or late stent thrombosis
    - FDA will be reviewing longer-term XIENCE V clinical data – out to three years
- Not all drug-eluting stents are the same.
  - Each factor associated with the system – the drug that is used, the rate of elution, the polymer coating, the stent platform and the delivery system – is important in overall clinical outcomes.

Future of DES market/implications for BMS:

- We don't believe the market will be significantly affected long-term.
  - Drug-eluting stents have been shown to benefit tens of thousands of clinical trial patients and millions of real-world patients, over many years.
  - We have an opportunity with next-generation solutions to improve upon current technology and medical practice to advance patient care over time.
- In the short-term, there may be some movement toward more use of bare metal stents.
  - We have seen a small uptick in bare metal stent sales over last few months.

- Abbott is the market leader in bare metal stents – with our VISION platform – so we are well-positioned in both areas.

Impact on Abbott's current forecast/models:

- Our assumptions for Abbott's DES business remain unchanged.

XIENCE V regulatory status:

- Approved and on the market in most countries in Europe and Asia Pacific.
- We have a robust clinical program that will support the preparation of a thorough data submission to the FDA.
- We remain on track for a U.S. launch of XIENCE V in early 2008.

Status of European launch:

- We launched in the majority of European countries in October.
- Additional countries are coming on board now and will continue into early 2007.
- Exceptions: France and Belgium (where reimbursement has not been finalized/ traditionally takes longer)
- Not getting into more specific details of our launch strategy for competitive reasons.
- *If pressed:* We've said in our plan that we expect peak year DES market share in the mid-high 20s.

Status of everolimus and FDA approval:

- Novartis has significant worldwide clinical data on the safety of everolimus in the setting of organ transplantation.
- Our filings require reference data from Novartis on everolimus, which has already been filed with the FDA.

Status of SPIRIT clinical trials

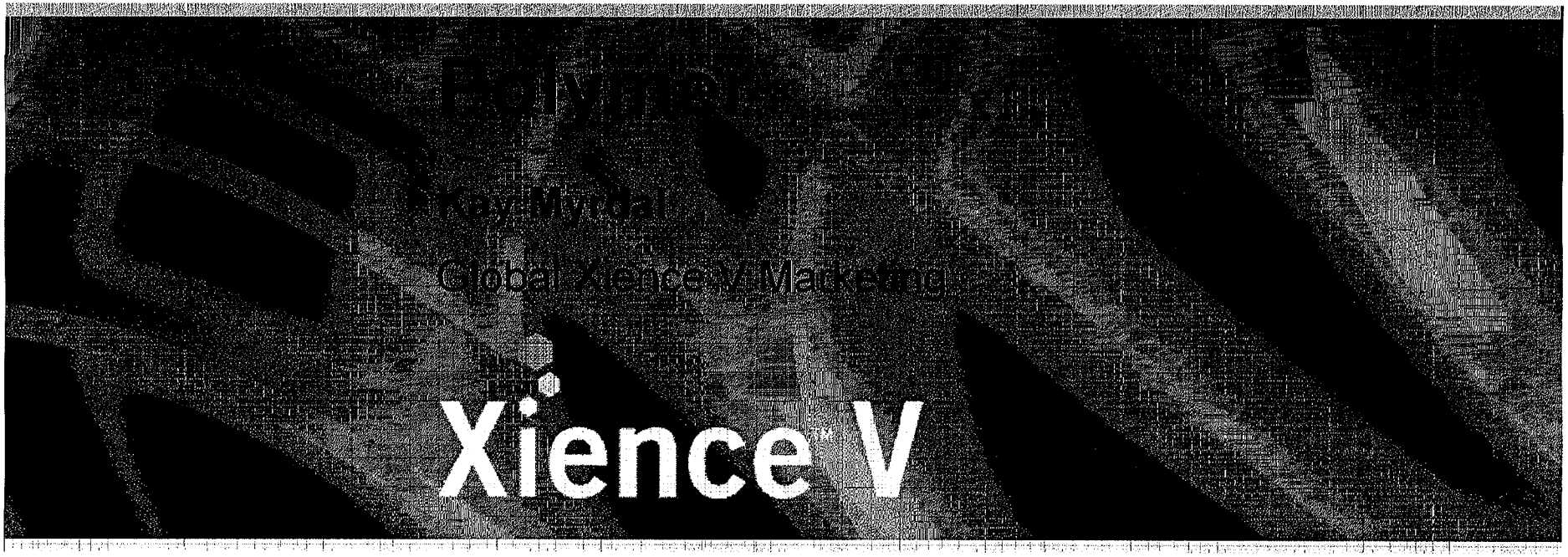
- Our SPIRIT family of trials will include approximately 10,000 patients with five years of follow-up
  - More than 4,500 [26+223+666+1,125+2,900=4,740] patients with clinical follow up by mid-2007; clinical data out to 3 years.
- ***If asked:*** At the time we file our final PMA module in 1H07, we'll have 3-year data from SPIRIT I, 18-mos. data from SPIRIT II; 9-mos. data from SPIRIT III. Providing FDA with ongoing safety data from SPIRIT IV and V during course of its review.

Enrollment update:

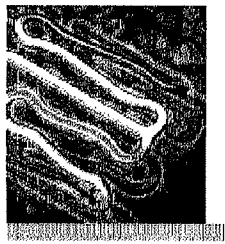
- SPIRIT First: ~60 patients (26 Xience; 28 Vision); completed enrollment 4/21/04; 3-year follow up 4/07.
- SPIRIT II: 300 patients (223 Xience; 77 Taxus); completed enrollment 11/10/05; 9-mos. follow up 10/06; 12-mos follow up 1H07.
- SPIRIT III: 1,002 U.S. patients in randomized cohort (668 Xience; 334 Taxus); completed enrollment 3/15/06; 9-mos data at ACC or PCR 1H07.

- SPIRIT IV: 1,125 patients (750 Xience; 375 Taxus); [more than 300] patients enrolled; enrollment completed by 1Q07.
- SPIRIT V: 3,000 patients total (2,700 Xience registry + 321 in diabetic arm (214 Xience; 107 Taxus)); approaching 400 patients enrolled; enrollment completed by 1H07.

XIENCE V Training



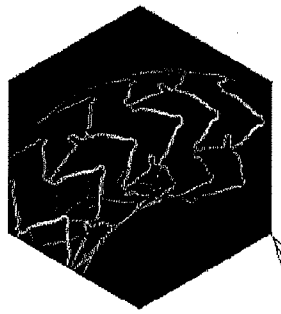
Abbott
A Promise for Life

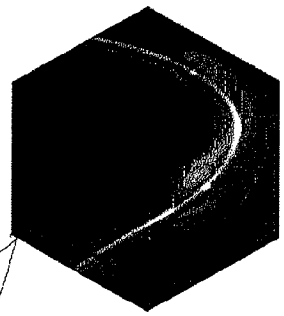


XIENCE V
State-of-the-Art Components

MULTI-LINK VISION
Stent

MULTI-LINK VISION
Stent Delivery System

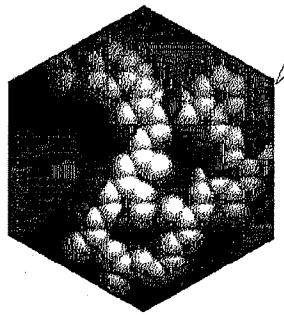


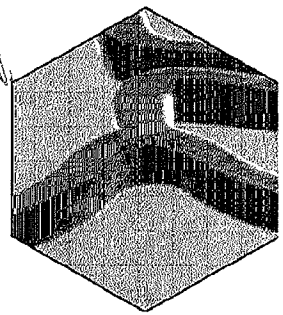


Deliverability

Efficacy

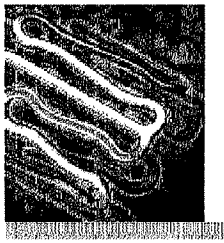
Safety





Everolimus

Polymer Coating



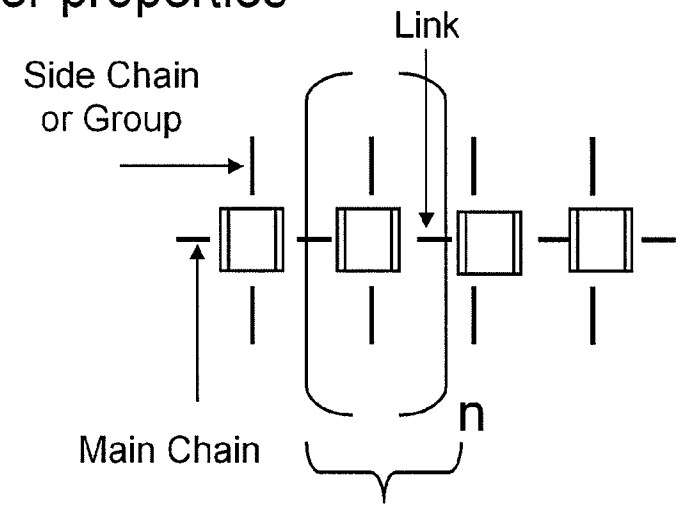
What is a polymer?

A polymer is a chain of molecules connected through simple links in the main chain

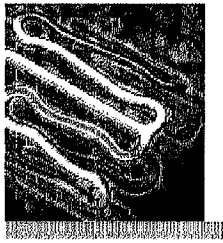
The polymer holds the drug and controls its release into the body

3 main things determine the polymer properties

- Type of units
- Number of units
- Links between the units



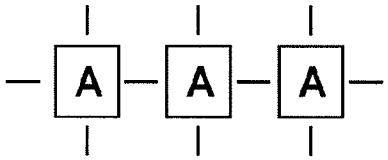
where n - # of repeating units



Polymer Designs

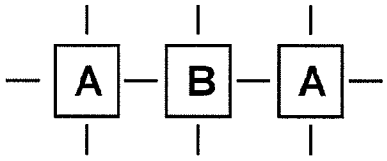
Homopolymer

- Single type of repeated units
- Less flexibility in achieving balance between elasticity and toughness



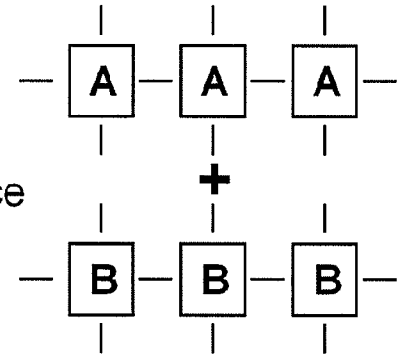
Copolymer

- Multiple types of repeated units
- Allows great flexibility in tailoring properties
- Type and ratio of the units selected determine the balance of elasticity & toughness



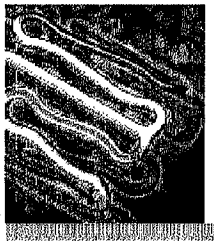
Polymer Blend

- Alternative method of achieving the desired balance of properties
- Challenge is consistency & manufacturability



Xience V

Abbott Vascular

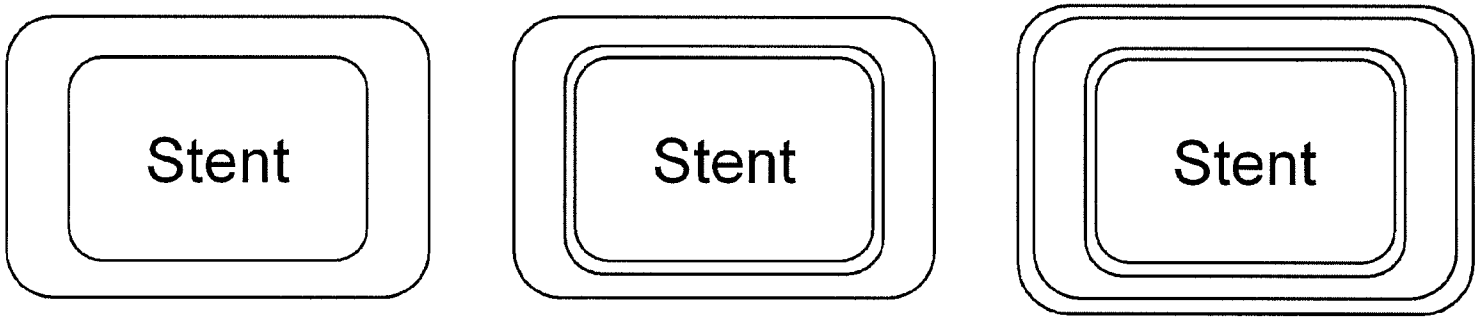


Polymer Coating Configurations

Primer: may be applied to improve adhesion to stent

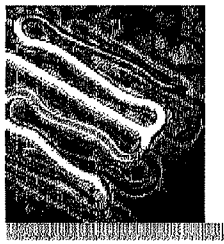
Matrix Coating: mixture of drug and polymer

Topcoat: may be applied if needed to slow the release rate of the drug



Matrix only Design ***Primer & Matrix Design*** ***Primer, Matrix & Topcoat Design***

Topcoat
Matrix
Primer



XIENCE V Polymer Coating

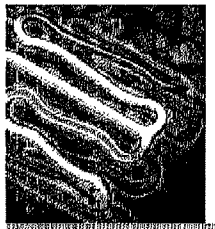
Type of Polymer: Acrylic and Fluorinated

Biocompatible

- Inert
- Previously proven and used in blood contacting applications

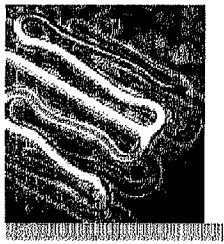
Matrix Polymer Design: Co-Polymer

- Made up of tough and elastic segments
- Choice and ratio of hard and soft segments dictate balance of:
  - Toughness
  - Elasticity



Properties of an Ideal DES Coating

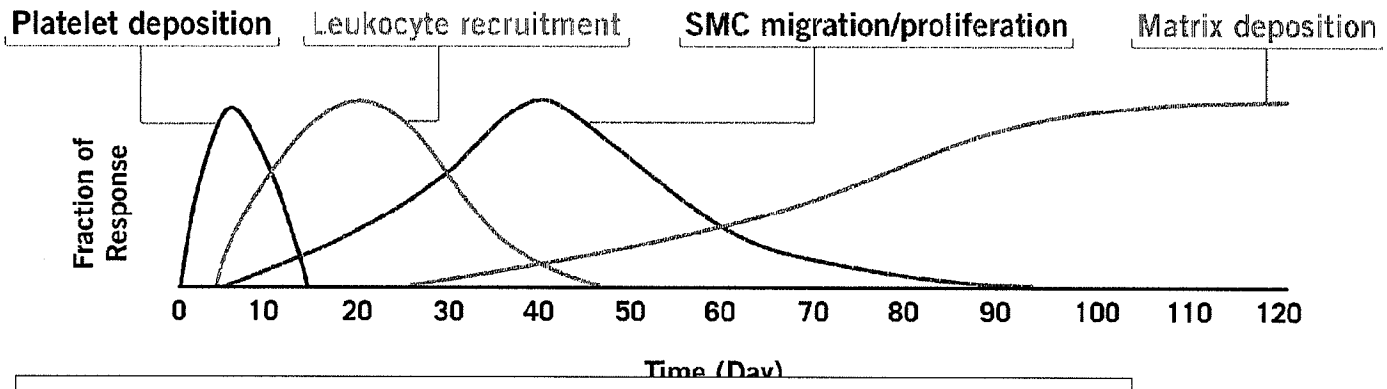
- ☑ Controlled release of the drug
  - Release throughout the restenosis cascade
  - Complete release of drug over time
- ☑ Biocompatibility
  - Non-thrombogenic and safe
  - Proven in other blood contacting applications
- ☑ High drug loading capacity
  - Thin coating thickness
  - Minimizes crossing profile
- ☑ Uniform Coating Integrity
  - Adhesion to stent, but no adhesion to balloon
  - Elastic for coating integrity upon expansion
  - Toughness for coating integrity during delivery



Controlled Release of Drug

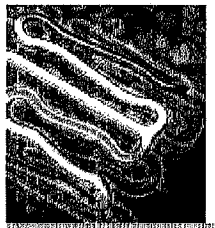
Why does the timeframe of drug release matter?

Restenosis Cascade

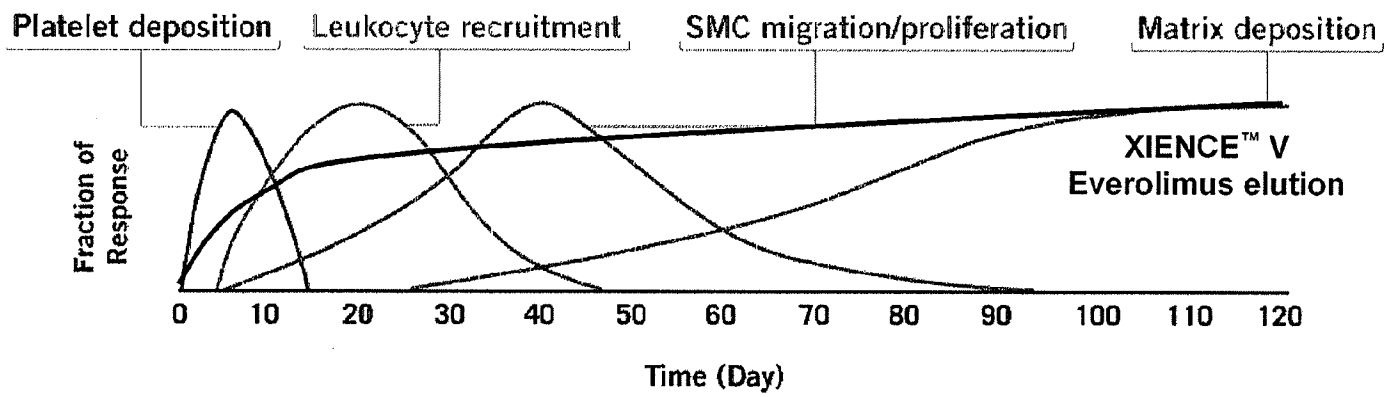


4 major biological processes contribute to restenosis post-implant

It is important for drug to release throughout the restenosis cascade



Controlled Release of Drug (cont)

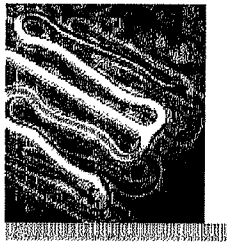


XIENCE™ V's polymer enables continuous release of Everolimus throughout the restenosis cascade for excellent clinical results

Based on pre-clinical data

References

1. A paradigm for restenosis based on cell biology: clues for the development of new preventive therapies. JS Forrester et al. J Am Coll Cardiol 1991, Vol 17, No 3: 758-69
2. D Simon, "Inflammation: The Key Element in the Biology of Restenosis." Inflammation Summit. TCT 2003
3. Data on file at Guidant

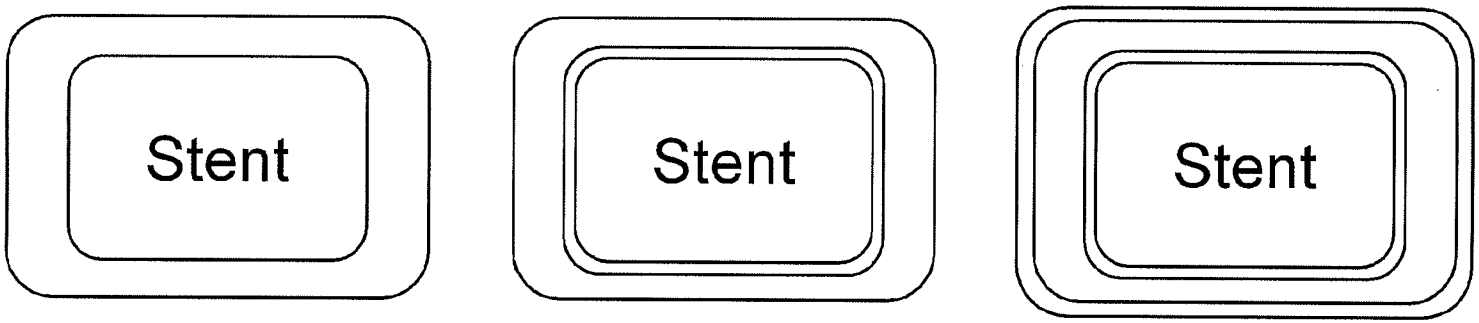


Polymer Coating Configurations

Primer: may be applied to improve adhesion to stent

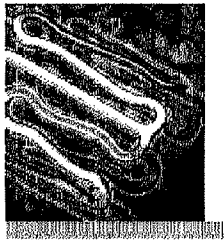
Matrix Coating: mixture of drug and polymer

Topcoat: may be applied if needed to slow the release rate of the drug



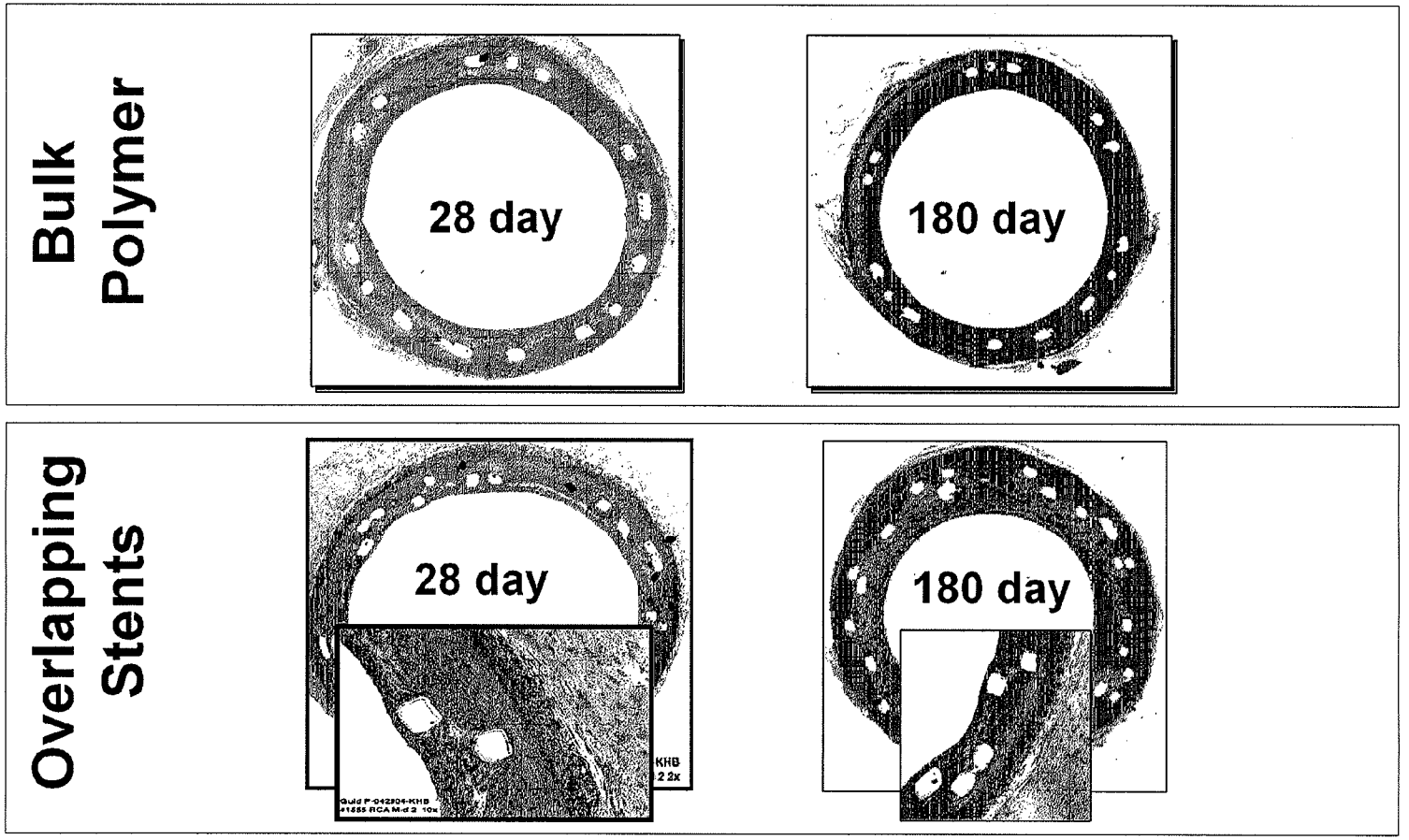
Matrix only Design ***Primer & Matrix Design*** ***Primer, Matrix & Topcoat Design***

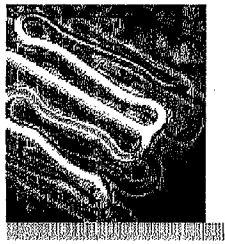
Topcoat
Matrix
Primer



Biocompatibility

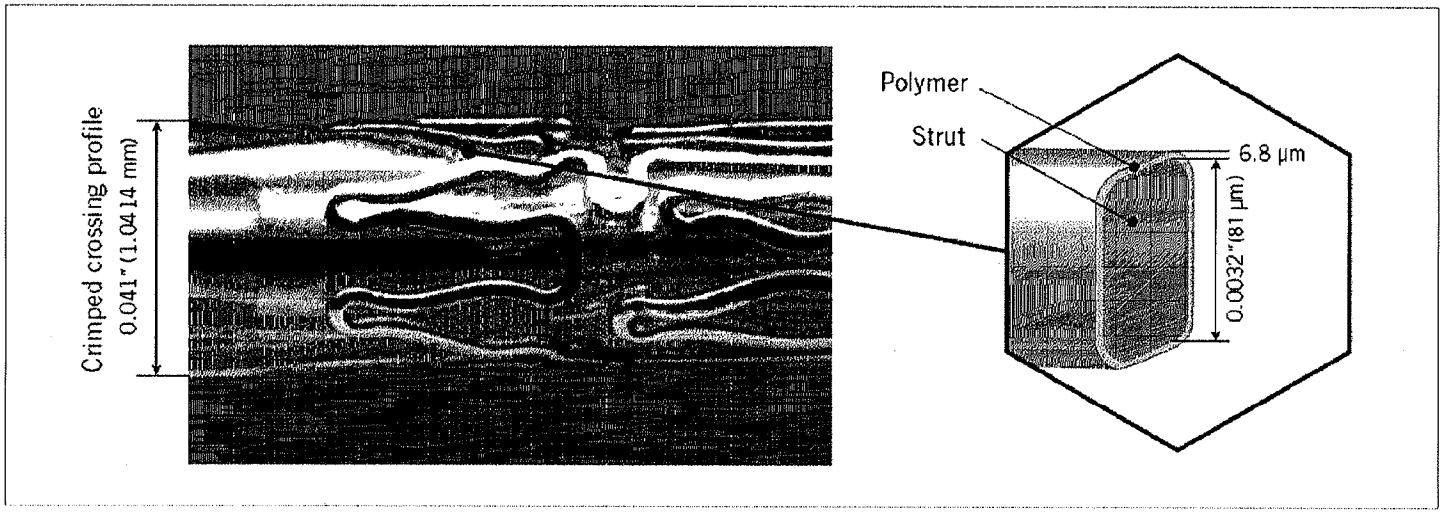
Pre-Clinical Evidence of Biocompatibility





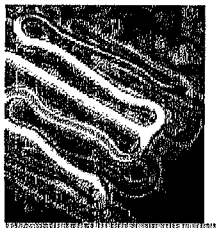
High Drug Loading Capacity

Ultra-thin coating maintains excellent crossing profile and deliverability



Polymer Thickness	**6.8 µm**
System Crossing Profile	**.041”**

Tests performed by and data available on file at Abbott Vascular

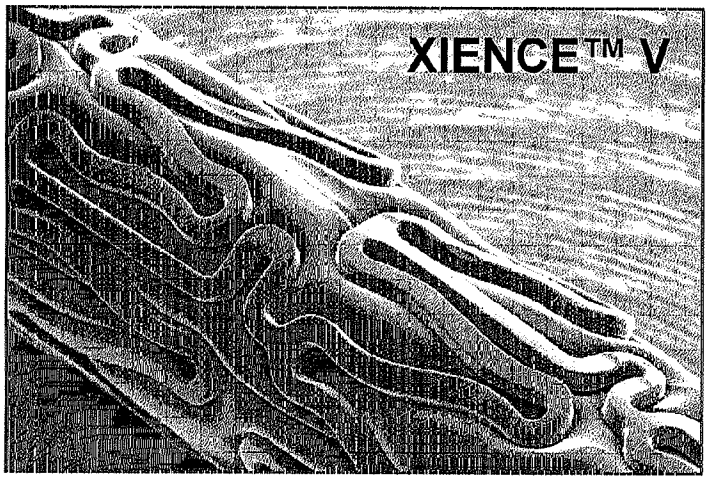


Uniform Coating Integrity

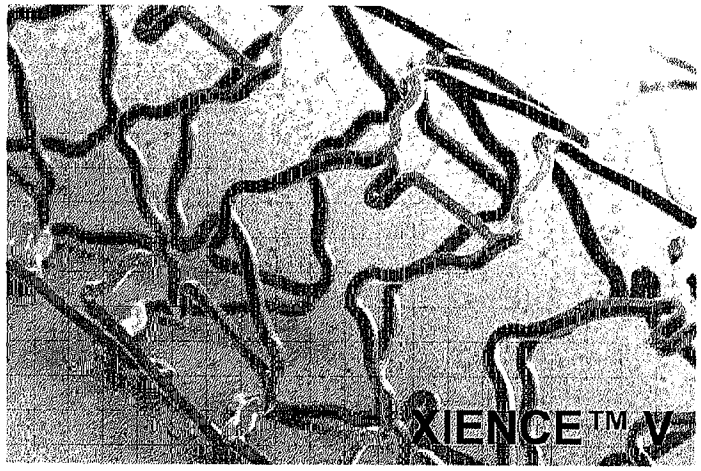
Excellent adhesion to stent

Non-tacky matrix prevents "unwanted" adhesions

Crimped system



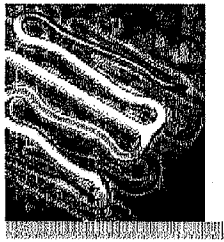
Post-expansion



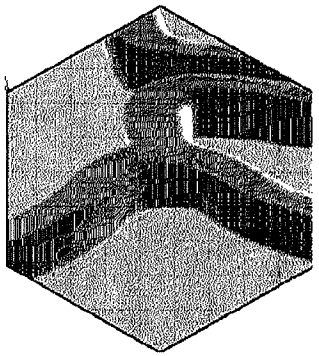
Elasticity: Ultimate elongation = 600-750%

Toughness: Shore D Hardness = 60

Photos taken by and on file at Abbott Vascular



XIENCE V Polymer



- ☑ **Controlled release of the drug**
  - Release throughout the restenosis cascade
  - Complete release of drug over time
- ☑ **Biocompatibility**
  - Non-thrombogenic and safe
  - Previously proven and used in blood contacting applications
- ☑ **High drug loading capacity**
  - Thin coating thickness
  - Minimizes crossing profile
- ☑ **Uniform Coating Integrity**
  - Adhesion to stent, but no adhesion to balloon
  - Elastic for coating integrity upon expansion
  - Toughness for coating integrity during delivery